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=> d his

     (FILE 'HOME' ENTERED AT 11:42:47 ON 13 FEB 2004)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 11:43:06 ON 13 FEB 2004
L1         23212 S "LDL RECEPTOR"
L2            14 S "LOW(A)DENSITY"
L3        237773 S LOW (A)DENSITY
L4        424929 S LIPOPROTEIN?
L5       3623226 S RECEPTOR?
L6         26576 S L4(A)L5
L7         18188 S L3(A)L6
L8           941 S "P42/44 MAPK"
L9            16 S L7 AND L8
L10            9 DUP REM L9 (7 DUPLICATES REMOVED)
L11           16 S L8 AND L6
L12            9 DUP REM L11 (7 DUPLICATES REMOVED)
L13           25 S L1 AND L8
L14           13 DUP REM L13 (12 DUPLICATES REMOVED)
                 E MEHTA K D/AU
L15          128 S E3
L16        32841 S L1 OR L7
L17           60 S L15 AND L16
L18           21 DUP REM L17 (39 DUPLICATES REMOVED)

=>
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NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	SEP 09	CA/CAplus records now contain indexing from 1907 to the present
NEWS 4	DEC 08	INPADOC: Legal Status data reloaded
NEWS 5	SEP 29	DISSABS now available on STN
NEWS 6	OCT 10	PCTFULL: Two new display fields added
NEWS 7	OCT 21	BIOSIS file reloaded and enhanced
NEWS 8	OCT 28	BIOSIS file segment of TOXCENTER reloaded and enhanced
NEWS 9	NOV 24	MSDS-CCOHS file reloaded
NEWS 10	DEC 08	CABA reloaded with left truncation
NEWS 11	DEC 08	IMS file names changed
NEWS 12	DEC 09	Experimental property data collected by CAS now available in REGISTRY
NEWS 13	DEC 09	STN Entry Date available for display in REGISTRY and CA/CAplus
NEWS 14	DEC 17	DGENE: Two new display fields added
NEWS 15	DEC 18	BIOTECHNO no longer updated
NEWS 16	DEC 19	CROPU no longer updated; subscriber discount no longer available
NEWS 17	DEC 22	Additional INPI reactions and pre-1907 documents added to CAS databases
NEWS 18	DEC 22	IFIPAT/IFIUDB/IFICDB reloaded with new data and search fields
NEWS 19	DEC 22	ABI-INFORM now available on STN
NEWS 20	JAN 27	Source of Registration (SR) information in REGISTRY updated and searchable
NEWS 21	JAN 27	A new search aid, the Company Name Thesaurus, available in CA/CAplus
NEWS 22	FEB 05	German (DE) application and patent publication number format changes

NEWS EXPRESS	DECEMBER 28 CURRENT WINDOWS VERSION IS V7.00, CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP), AND CURRENT DISCOVER FILE IS DATED 23 SEPTEMBER 2003
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

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=> file medline embase biosis biotechds scisearch hcaplus ntis lifesci
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
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FILE 'LIFESCI' ENTERED AT 11:43:06 ON 13 FEB 2004
COPYRIGHT (C) 2004 Cambridge Scientific Abstracts (CSA)


=> s "LDL receptor"
L1        23212 "LDL RECEPTOR"

=> s "low(a)density"
L2           14 "LOW(A)DENSITY"

=> s low (a)density
L3       237773 LOW (A) DENSITY

=> s lipoprotein?
L4       424929 LIPOPROTEIN?

=> s receptor?
L5      3623226 RECEPTOR?

=> s l4(a)l5
L6        26576 L4(A) L5

=> s l3(a)l6
L7        18188 L3(A) L6

=> s "p42/44 MAPK"
L8          941 "P42/44 MAPK"

=> s l7 and l8
L9           16 L7 AND L8
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=> dup rem l9
PROCESSING COMPLETED FOR L9
L10 9 DUP REM L9 (7 DUPLICATES REMOVED)

=> d 1-9 ibib ab

L10 ANSWER 1 OF 9 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN DUPLICATE 1
ACCESSION NUMBER: 2003420685 EMBASE
TITLE: pp90(RSK)- and protein kinase C-dependent pathway regulates **p42/44(MAPK)**-induced LDL receptor transcription in HepG2 cells.
AUTHOR: Kapoor G.S.; Golden C.; Atkins B.; Mehta K.D.
CORPORATE SOURCE: K.D. Mehta, Dept. of Molec./Cell. Biochemistry, Ohio State University, Coll. of Medicine and Public Health, 1645 Neil Ave., Columbus, OH 43210, United States. mehta.80@osu.edu
SOURCE: Journal of Lipid Research, (2003) 44/3 (584-593).
Refs: 46
ISSN: 0022-2275 CODEN: JLPRAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We have previously shown that different extracellular stimuli require signaling through the Raf/MEK/**p42/ 44(MAPK)** cascade to induce LDL receptor expression. The present studies were designed to delineate the molecular mechanisms underlying **p42/ 44(MAPK)**-induced LDL receptor transcription in HepG2-ΔRaf-1:ER cells, a modified HepG2 cell line in which the Raf-1/MEK/**p42/44(MAPK)** cascade can be specifically activated by anti-estradiol ICI182,780 in an agonist-specific manner. Using these cells, we show that: a) LDL receptor induction was reduced in reporter constructs containing mutation in either Sp1 or sterol-regulatory element-1 (SRE-1) sites, whereas inactivation of both sites abolished the induction; b) E1A, which inhibits CREB binding protein (CBP), a common activator of SRE-1 binding protein and Sp1, strongly repressed the induction; c) intracellular inhibition of the 90 kDa ribosomal S6 kinase (pp90(RSK)) cascade reduced LDL receptor induction; d) highly selective protein kinase C (PKC) inhibitors effectively abrogated the induction without affecting activation of pp90 (RSK); and e) overexpression of PKCβ significantly induced LDL receptor promoter activity. Taken together, these results demonstrate that pp90(RSK) and PKCβ are downstream effectors and Sp1, SRE-1 binding protein, and CBP are part of the transcriptional complex resulting in induction of LDL receptor expression in response to activation of the Raf/MEK/**p42 /44(MAPK)** cascade. These findings identify for the first time a role for PKCβ in determining the specificity of **p42/44 (MAPK)** signaling by participating with pp90(RSK) in regulating gene expression.

L10 ANSWER 2 OF 9 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2002270304 MEDLINE
DOCUMENT NUMBER: 21993139 PubMed ID: 11997513
TITLE: Critical role of diacylglycerol- and phospholipid-regulated protein kinase C epsilon in induction of **low-density lipoprotein receptor** transcription in response to depletion of cholesterol.
AUTHOR: Mehta Kamal D; Radominska-Pandya Anna; Kapoor Gurpreet S; Dave Bhuvanesh; Atkins Brett A
CORPORATE SOURCE: Department of Molecular and Cellular Biochemistry, The Ohio State University College of Medicine, Columbus, Ohio 43210, USA.. mehta.80@osu.edu

CONTRACT NUMBER: DK56226 (NIDDK)
R01 HL67760 (NHLBI)
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2002 Jun) 22 (11) 3783-93.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020516
Last Updated on STN: 20020611
Entered Medline: 20020606

AB Induction of low-density lipoprotein (LDL) receptor transcription in response to depletion of cellular sterols in animal cells is well established. The intracellular signal or signals involved in regulating this process, however, remain unknown. Using a specific inhibitor of protein kinase C (PKC), calphostin C, we show the requirement of this kinase in the induction process in human hepatoma HepG2 cells. Overexpression of PKC epsilon, but not PKC alpha, -gamma, -delta, or -zeta was found to dramatically induce (approximately 18-fold) LDL receptor promoter activity. Interestingly, PKC epsilon-mediated induction was found to be sterol resistant. To further establish that PKC epsilon is involved in the sterol regulation of LDL receptor gene transcription, endogenous PKC epsilon was specifically inhibited by transfection with antisense PKC epsilon phosphorothionate oligonucleotides. Antisense treatment decreased endogenous PKC epsilon protein levels and completely blocked induction of LDL receptor transcription following sterol depletion. PKC epsilon-induced LDL receptor transcription is independent of the extracellular signal-regulated kinase 1 and 2 (**p42/44(MAPK)**) cascade, because the MEK-1/2 inhibitor, PD98059 did not inhibit, even though it blocked **p42/44 (MAPK)** activation. Finally, photoaffinity labeling studies showed an isoform-specific interaction between PKC epsilon and sterols, suggesting that sterols may directly modulate its function by hampering binding of activators. This was confirmed by PKC activity assays. Altogether, these results define a novel signaling pathway leading to induction of LDL receptor transcription following sterol depletion, and a model is proposed to account for a new function for PKC epsilon as part of a sterol-sensitive signal transduction pathway in hepatic cells.

L10 ANSWER 3 OF 9 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN DUPLICATE 3
ACCESSION NUMBER: 2002274870 EMBASE
TITLE: Role of mitogen-activated protein kinases and protein kinase C in regulating **low-density lipoprotein receptor** expression.
AUTHOR: Mehta K.D.
CORPORATE SOURCE: K.D. Mehta, Department of Cellular Biochemistry, Ohio State Univ. College of Medicine, Columbus, OH 43210, United States. mehta.80@osu.edu
SOURCE: Gene Expression, (2002) 10/4 (153-164).
Refs: 95
ISSN: 1052-2166 CODEN: GEEXEJ
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The cell signaling pathways that culminate in induction of low-density lipoprotein (LDL) receptor transcription in response to a variety of extracellular and intracellular signals are beginning to be defined. Evidence is accumulating that LDL receptor transcription is under complex regulation and that a major pathway of induction by cytokines, growth factors, anisomycin, and phorbol esters involves the extracellular/mitogen-

activated protein kinase (**p42/44(MAPK)**)
cascade. In fact, degree **p42/44(MAPK)**
activation determines the extent of LDL receptor induction. The
suppression of LDL receptor expression by stress-activated p38(MAPK) via
p42/44(MAPK) provides a potential mechanism
for stress-induced hypercholesterolemia observed in humans and animals.
Moreover, endogenous signals such as cholesterol regulate LDL receptor
transcription through a different signaling cascade involving protein
kinase Cε isoform (PKCε). The ability of cholesterol to
directly bind PKCε in an isoform-specific manner strongly supports
its role in sensing the cellular cholesterol levels. The emerging picture
from the above studies is that regulation of LDL receptor transcription
results from the activity of a number of interlinked regulatory molecules
and pathways, rather than from a single linear series of events. These
studies will provide the necessary framework for understanding
differential responses within human populations to atherosclerosis
following high-fat/cholesterol diet. This information may also provide new
strategies to modulate specific gene expression with the hope to develop
novel therapies for the treatment of hypercholesterolemia.

L10 ANSWER 4 OF 9 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN DUPLICATE 4

ACCESSION NUMBER: 2002279144 EMBASE
TITLE: Activation of Raf-1/MEK-1/2/**p42/44(MAPK)** cascade alone is sufficient to uncouple LDL receptor expression from cell growth.
AUTHOR: Kapoor G.S.; Atkins B.A.; Mehta K.D.
CORPORATE SOURCE: K.D. Mehta, Dept. of Molecular/Cell. Biochemist., Ohio State Univ. College Medicine, 464 Hamilton Hall, 1645 Neil Avenue, Columbus, OH 43210, United States. mehta.80@osu.edu
SOURCE: Molecular and Cellular Biochemistry, (2002) 236/1-2 (13-22).
Refs: 36
ISSN: 0300-8177 CODEN: MCBIB8
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Our previous observation that induction of low density lipoprotein (LDL) receptor expression by a variety of extracellular signals is blocked by PD98059, a specific mitogen-activated protein kinase kinase inhibitor, led to the suggestion that the growth-responsive **p42/44(MAPK)** cascade plays a critical role in regulating LDL receptor transcription. To analyze the specific contribution of the **p42/44(MAPK)** cascade in regulating cell growth and LDL receptor induction, we established a HepG2-derived cell line that stably expresses an inducible form of oncogenic human Raf-1 kinase. Using this system, we provide direct evidence that specific activation of this cascade alone is not only required but is sufficient to fully induce LDL receptor expression. Interestingly, degree of **p42/44(MAPK)** activation determines the extent of LDL receptor induction. However, activation of **p42/44(MAPK)** in the above cells led to the inhibition of DNA synthesis, caused growth arrest, decrease in cyclin A and upregulation of p21(Cip) expression in a time-dependent manner. These results suggest that each of these two processes can be regulated independently of each other in response to **p42/44(MAPK)** activation. Thus, extent of **p42/44(MAPK)** activation may be important in transducing divergent cellular responses in human cells with implications for altered signaling resulting in hypercholesterolemia.

L10 ANSWER 5 OF 9 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

ACCESSION NUMBER: 2000226341 EMBASE
TITLE: Inhibition of stress-activated p38 mitogen-activated protein kinase induces **low-density lipoprotein receptor** expression.
AUTHOR: Mehta K.D.; Miller L.
CORPORATE SOURCE: K.D. Mehta, Dept. Biochemistry/Molecular Biology, College of Medicine, University of Arkansas, 4301 West Markham, Little Rock, AR 72205, United States
SOURCE: Trends in Cardiovascular Medicine, (2000) 9/7 (201-205). Refs: 38
ISSN: 1050-1738 CODEN: TCMDEQ
PUBLISHER IDENT.: S 1050-1738(00)00021-9
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
025 Hematology
029 Clinical Biochemistry
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We have recently shown that different signal transduction pathways initiated by a variety of agents converge on growth-responsive **p42/44(MAPK)** signaling cascade to induce low-density lipoprotein (LDL) receptor expression. Our recent demonstration that stress-activated p38(MAPK) negatively regulates LDL receptor expression in an isoform-specific manner via modulation of **p42/44(MAPK)** cascade represents a new dimension of complexity in the molecular communication that governs LDL receptor expression. The suggested one-way communication between p38(MAPK) and **p42/44(MAPK)** provides a potential mechanism for fine-tuning cellular levels of cholesterol in response to a diverse set of environmental cues, including stress. Cross talk between MAPKs opens new avenues toward understanding a variety of pathogenic processes; this makes them tempting targets for therapeutic interventions in cardiovascular diseases. Copyright (C) 1999 Elsevier Science Inc.

L10 ANSWER 6 OF 9 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 1999321880 MEDLINE
DOCUMENT NUMBER: 99321880 PubMed ID: 10391894
TITLE: One-way cross-talk between p38(MAPK) and **p42/44(MAPK)**. Inhibition of p38(MAPK) induces **low density lipoprotein receptor** expression through activation of the **p42/44(MAPK)** cascade.
AUTHOR: Singh R P; Dhawan P; Golden C; Kapoor G S; Mehta K D
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205, USA.
CONTRACT NUMBER: HL-51592 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Jul 9) 274 (28) 19593-600.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990816
Last Updated on STN: 20000303
Entered Medline: 19990805
AB In this paper, we report that SB202190 alone, a specific inhibitor of p38(MAPK), induces low density lipoprotein (LDL) receptor expression (6-8-fold) in a sterol-sensitive manner in HepG2 cells. Consistent with

this finding, selective activation of the p38(MAPK) signaling pathway by expression of MKK6b(E), a constitutive activator of p38(MAPK), significantly reduced LDL receptor promoter activity. Expression of the p38(MAPK) alpha-isoform had a similar effect, whereas expression of the p38(MAPK) betaII-isoform had no significant effect on LDL receptor promoter activity. SB202190-dependent increase in LDL receptor expression was accompanied by induction of **p42/44(MAPK**), and inhibition of this pathway completely prevented SB202190-induced LDL receptor expression, suggesting that p38(MAPK) negatively regulates the **p42/44(MAPK)** cascade and the responses mediated by this kinase. Cross-talk between these kinases appears to be one-way because modulation of **p42/44(MAPK)** activity did not affect p38(MAPK) activation by a variety of stress inducers. Taken together, these findings reveal a hitherto unrecognized one-way communication that exists between p38(MAPK) and **p42/44(MAPK)** and provide the first evidence that through the **p42/44(MAPK)** signaling cascade, the p38(MAPK) alpha-isoform negatively regulates LDL receptor expression, thus representing a novel mechanism of fine tuning cellular levels of cholesterol in response to a diverse set of environmental cues.

L10 ANSWER 7 OF 9 EMBASE on STN

ACCESSION NUMBER: 1999354593 EMBASE

TITLE: Critical role of **p42/44(MAPK)** activation in anisomycin and hepatocyte growth factor-induced LDL receptor expression: Activation of Raf-1/MEK- 1/**p42/44(MAPK)** cascade alone is sufficient to induce LDL receptor expression.

AUTHOR: Dhawan P.; Bell A.; Kumar A.; Golden C.; Mehta K.D.

CORPORATE SOURCE: K.D. Mehta, Biochemistry/Molecular Biology Dept., College of Medicine, Univ. of Arkansas for Med. Sciences, 4301 West Markham, Little Rock, AR 72205, United States. mehtakamald@exchange.uams.edu

SOURCE: Journal of Lipid Research, (1999) 40/10 (1911-1919). Refs: 37
ISSN: 0022-2275 CODEN: JLPRAW

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 029 Clinical Biochemistry
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The protein synthesis inhibitor anisomycin activates stress-related mitogen-activated protein kinases (MAPKs), namely, c-jun NH2-terminal kinase (p46/54(JNK)) and p38(MAPK) in mammalian cells. In this paper, we show that although exposure to anisomycin resulted in rapid and strong activation of p46/54(JNK) and p38(MAPK), with a delayed low level dual-phosphorylation of mitogen/extracellular protein kinase (**p42/44(MAPK)**), low density lipoprotein (LDL) receptor induction depends solely on the mild activation of **p42/44(MAPK)** signaling cascade in HepG2 cells. Unlike hepatocyte growth factor (HGF) which caused LDL receptor induction via rapid, strong, and Ras- dependent **p42/44(MAPK**) activation, anisomycin-induced **p42/44(MAPK**) activity and increased LDL receptor expression in a Ras-independent manner. Finally, we examined the role of the **p42/44(MAPK)** signaling cascade in LDL receptor induction by activating this kinase independently of anisomycin or HGF. By using estrogen-dependent human Raf-1 protein kinase in transient transfection assays, we show that the exclusive activation of the Raf-1/MEK-1/**p42/44(MAPK)** signaling cascade with antiestrogen ICI 182,780 caused induction of LDL receptor expression to

the same level as observed with either HGF or anisomycin. Consistent with the role of **p42/44(MAPK)**, induction was strongly inhibited by pretreatment with the MEK-1/2 inhibitor PD98059. Our observation that anisomycin can use **p42/44(MAPK)** signaling cascade is a departure from established thinking, and the results presented shows that activation of the **p42/44(MAPK)** alone is sufficient to fully induce LDL receptor transcription.

L10 ANSWER 8 OF 9 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2000:468792 SCISEARCH
THE GENUINE ARTICLE: 325ZV
TITLE: Inhibition of stress-activated p38 mitogen-activated protein kinase induces **low-density lipoprotein receptor** expression
AUTHOR: Mehta K D (Reprint); Miller L
CORPORATE SOURCE: UNIV ARKANSAS MED SCI, COLL MED, DEPT BIOCHEM & MOL BIOL, SLOT 516, 4301 W MARKHAM, LITTLE ROCK, AR 72205 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: TRENDS IN CARDIOVASCULAR MEDICINE, (OCT 1999) Vol. 9, No. 7, pp. 201-205.
Publisher: ELSEVIER SCIENCE LONDON, 84 THEOBALDS RD, LONDON WC1X 8RR, ENGLAND.
ISSN: 1050-1738.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 38
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We have recently shown that different signal transduction. pathways initiated by a variety of agents converge on growth-responsive **p42/44(MAPK)** signaling cascade to induce low-density lipoprotein (LDL) receptor expression. Our recent demonstration that stress-activated p38(MAPK) negatively regulates LDL receptor expression in an isoform-specific manner via modulation of **p42/44(MAPK)** cascade represents a view dimension of complexity in. the molecular communication that governs LDL receptor expression. The suggested one-way communication between p38(MAPK) and **p42/44(MAPK)** provides a potential mechanism for fine-tuning cellular levels of cholesterol in response to a diverse set of environmental cues, including stress. Cross talk between MAPKs opens new avenues toward understanding a variety of pathogenic processes; this makes them tempting targets for therapeutic interventions in cardiovascular diseases. (Trends Cardiovasc Med 1999;9:201-205), (C) 1999, Elsevier Science Inc.

L10 ANSWER 9 OF 9 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1999:167257 BIOSIS
DOCUMENT NUMBER: PREV199900167257
TITLE: LDL receptor expression is regulated positively by P42/44MAPK pathway in hepatic cells.
AUTHOR(S): Dhawan, P. [Reprint author]; McMahon, M.; Mehta, K. D. [Reprint author]
CORPORATE SOURCE: Dep. Biochemistry Molecular Biology, Univ. Ark. Med. Sciencdes 4301, West Markham St., Littlerock, AR 72205, USA
SOURCE: FASEB Journal, (March 12, 1999) Vol. 13, No. 4 PART 1, pp. A194. print.
Meeting Info.: Annual Meeting of the Professional Research Scientists for Experimental Biology 99. Washington, D.C., USA. April 17-21, 1999.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English

ENTRY DATE: Entered STN: 19 Apr 1999
Last Updated on STN: 19 Apr 1999

=> d his

(FILE 'HOME' ENTERED AT 11:42:47 ON 13 FEB 2004)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 11:43:06 ON 13 FEB 2004

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L1         23212 S "LDL RECEPTOR"
L2            14 S "LOW(A)DENSITY"
L3        237773 S LOW (A)DENSITY
L4        424929 S LIPOPROTEIN?
L5       3623226 S RECEPTOR?
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L7         18188 S L3(A)L6
L8           941 S "P42/44 MAPK"
L9            16 S L7 AND L8
L10            9 DUP REM L9 (7 DUPLICATES REMOVED)

=> s l8 and l6
L11           16 L8 AND L6

=> dup rem l11
PROCESSING COMPLETED FOR L11
L12            9 DUP REM L11 (7 DUPLICATES REMOVED)

=> d 1-9 ibib
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L12 ANSWER 1 OF 9 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN DUPLICATE 1

ACCESSION NUMBER: 2003420685 EMBASE
TITLE: pp90(RSK)- and protein kinase C-dependent pathway regulates **p42/44(MAPK)**-induced LDL receptor transcription in HepG2 cells.
AUTHOR: Kapoor G.S.; Golden C.; Atkins B.; Mehta K.D.
CORPORATE SOURCE: K.D. Mehta, Dept. of Molec./Cell. Biochemistry, Ohio State University, Coll. of Medicine and Public Health, 1645 Neil Ave., Columbus, OH 43210, United States. mehta.80@osu.edu
SOURCE: Journal of Lipid Research, (2003) 44/3 (584-593).
Refs: 46
ISSN: 0022-2275 CODEN: JLPRAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

L12 ANSWER 2 OF 9 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2002270304 MEDLINE
DOCUMENT NUMBER: 21993139 PubMed ID: 11997513
TITLE: Critical role of diacylglycerol- and phospholipid-regulated protein kinase C epsilon in induction of low-density **lipoprotein receptor** transcription in response to depletion of cholesterol.
AUTHOR: Mehta Kamal D; Radominska-Pandya Anna; Kapoor Gurpreet S; Dave Bhuvanesh; Atkins Brett A
CORPORATE SOURCE: Department of Molecular and Cellular Biochemistry, The Ohio State University College of Medicine, Columbus, Ohio 43210, USA.. mehta.80@osu.edu
CONTRACT NUMBER: DK56226 (NIDDK)
R01 HL67760 (NHLBI)

SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2002 Jun) 22 (11) 3783-93.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020516
Last Updated on STN: 20020611
Entered Medline: 20020606

L12 ANSWER 3 OF 9 on STN EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. DUPLICATE 3
ACCESSION NUMBER: 2002274870 EMBASE
TITLE: Role of mitogen-activated protein kinases and protein kinase C in regulating low-density **lipoprotein receptor** expression.
AUTHOR: Mehta K.D.
CORPORATE SOURCE: K.D. Mehta, Department of Cellular Biochemistry, Ohio State Univ. College of Medicine, Columbus, OH 43210, United States. mehta.80@osu.edu
SOURCE: Gene Expression, (2002) 10/4 (153-164).
Refs: 95
ISSN: 1052-2166 CODEN: GEEXEJ
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

L12 ANSWER 4 OF 9 on STN EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. DUPLICATE 4
ACCESSION NUMBER: 2002279144 EMBASE
TITLE: Activation of Raf-1/MEK-1/2/**p42/44**(**MAPK**) cascade alone is sufficient to uncouple LDL receptor expression from cell growth.
AUTHOR: Kapoor G.S.; Atkins B.A.; Mehta K.D.
CORPORATE SOURCE: K.D. Mehta, Dept. of Molecular/Cell. Biochemist., Ohio State Univ. College Medicine, 464 Hamilton Hall, 1645 Neil Avenue, Columbus, OH 43210, United States. mehta.80@osu.edu
SOURCE: Molecular and Cellular Biochemistry, (2002) 236/1-2 (13-22).
Refs: 36
ISSN: 0300-8177 CODEN: MCBIB8
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

L12 ANSWER 5 OF 9 on STN EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
ACCESSION NUMBER: 2000226341 EMBASE
TITLE: Inhibition of stress-activated p38 mitogen-activated protein kinase induces low-density **lipoprotein receptor** expression.
AUTHOR: Mehta K.D.; Miller L.
CORPORATE SOURCE: K.D. Mehta, Dept. Biochemistry/Molecular Biology, College of Medicine, University of Arkansas, 4301 West Markham, Little Rock, AR 72205, United States
SOURCE: Trends in Cardiovascular Medicine, (2000) 9/7 (201-205).
Refs: 38
ISSN: 1050-1738 CODEN: TCMDEQ
PUBLISHER IDENT.: S 1050-1738(00)00021-9

COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
025 Hematology
029 Clinical Biochemistry
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English

L12 ANSWER 6 OF 9 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 1999321880 MEDLINE
DOCUMENT NUMBER: 99321880 PubMed ID: 10391894
TITLE: One-way cross-talk between p38(MAPK) and **p42/44(MAPK)**. Inhibition of p38(MAPK) induces low density **lipoprotein receptor** expression through activation of the **p42/44(MAPK)** cascade.
AUTHOR: Singh R P; Dhawan P; Golden C; Kapoor G S; Mehta K D
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205, USA.
CONTRACT NUMBER: HL-51592 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Jul 9) 274 (28) 19593-600.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990816
Last Updated on STN: 20000303
Entered Medline: 19990805

L12 ANSWER 7 OF 9 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 1999354593 EMBASE
TITLE: Critical role of **p42/44(MAPK)** activation in anisomycin and hepatocyte growth factor-induced LDL receptor expression: Activation of Raf-1/MEK- 1/**p42/44(MAPK)** cascade alone is sufficient to induce LDL receptor expression.
AUTHOR: Dhawan P.; Bell A.; Kumar A.; Golden C.; Mehta K.D.
CORPORATE SOURCE: K.D. Mehta, Biochemistry/Molecular Biology Dept., College of Medicine, Univ. of Arkansas for Med. Sciences, 4301 West Markham, Little Rock, AR 72205, United States. mehtakamald@exchange.uams.edu
SOURCE: Journal of Lipid Research, (1999) 40/10 (1911-1919).
Refs: 37
ISSN: 0022-2275 CODEN: JLPRAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

L12 ANSWER 8 OF 9 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2000:468792 SCISEARCH
THE GENUINE ARTICLE: 325ZV
TITLE: Inhibition of stress-activated p38 mitogen-activated protein kinase induces low-density **lipoprotein**

receptor expression
AUTHOR: Mehta K D (Reprint); Miller L
CORPORATE SOURCE: UNIV ARKANSAS MED SCI, COLL MED, DEPT BIOCHEM & MOL BIOL, SLOT 516, 4301 W MARKHAM, LITTLE ROCK, AR 72205 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: TRENDS IN CARDIOVASCULAR MEDICINE, (OCT 1999) Vol. 9, No. 7, pp. 201-205.
Publisher: ELSEVIER SCIENCE LONDON, 84 THEOBALDS RD, LONDON WC1X 8RR, ENGLAND.
ISSN: 1050-1738.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 38
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 9 OF 9 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1999:167257 BIOSIS
DOCUMENT NUMBER: PREV199900167257
TITLE: LDL receptor expression is regulated positively by P42/44MAPK pathway in hepatic cells.
AUTHOR(S): Dhawan, P. [Reprint author]; McMahon, M.; Mehta, K. D. [Reprint author]
CORPORATE SOURCE: Dep. Biochemistry Molecular Biology, Univ. Ark. Med. Sciencdes 4301, West Markham St., Littlerock, AR 72205, USA
SOURCE: FASEB Journal, (March 12, 1999) Vol. 13, No. 4 PART 1, pp. A194. print.
Meeting Info.: Annual Meeting of the Professional Research Scientists for Experimental Biology 99. Washington, D.C., USA. April 17-21, 1999.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Apr 1999
Last Updated on STN: 19 Apr 1999

=> d his

(FILE 'HOME' ENTERED AT 11:42:47 ON 13 FEB 2004)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 11:43:06 ON 13 FEB 2004
L1 23212 S "LDL RECEPTOR"
L2 14 S "LOW(A)DENSITY"
L3 237773 S LOW (A)DENSITY
L4 424929 S LIPOPROTEIN?
L5 3623226 S RECEPTOR?
L6 26576 S L4(A)L5
L7 18188 S L3(A)L6
L8 941 S "P42/44 MAPK"
L9 16 S L7 AND L8
L10 9 DUP REM L9 (7 DUPLICATES REMOVED)
L11 16 S L8 AND L6
L12 9 DUP REM L11 (7 DUPLICATES REMOVED)

=> s l1 and l8
L13 25 L1 AND L8

=> dup rem l13
PROCESSING COMPLETED FOR L13
L14 13 DUP REM L13 (12 DUPLICATES REMOVED)

=> d 1-13 ibib ab

L14 ANSWER 1 OF 13 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2003:633436 SCISEARCH
THE GENUINE ARTICLE: 701YF
TITLE: LDL immune complexes stimulate **LDL receptor** expression in U937 histiocytes via extracellular signal-regulated kinase and AP-1
AUTHOR: Fu Y C; Huang Y; Bandyopadhyay S; Virella G; Lopes-Virella M F (Reprint)
CORPORATE SOURCE: Raplh H Johnson Vet Adm Med Ctr, Charleston, SC 29401 USA (Reprint); Med Univ S Carolina, Div Endocrinol Diabet & Med Genet, Dept Med, Charleston, SC 29425 USA; Med Univ S Carolina, Dept Immunol & Microbiol, Charleston, SC 29425 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF LIPID RESEARCH, (JUL 2003) Vol. 44, No. 7, pp. 1315-1321.
Publisher: LIPID RESEARCH INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 USA.
ISSN: 0022-2275.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 21
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We have previously shown that LDL-containing immune complexes (LDL-ICs) induce up-regulation of **LDL receptor** (LDLR) expression in human macrophages. The present study further investigated the molecular mechanisms leading to LDLR up-regulation by LDI-ICs as well as the signaling pathways involved. Results showed that treatment of U937 histiocytes with LDL-ICs did not increase the precursors and the cleaved forms of sterol-regulatory element binding proteins (SREBPs) la and 2, suggesting that SREBPs may not be involved in LDLR up-regulation by LDIrICs. Promoter deletion and mutation studies showed that the AP-1 binding sites were essential for LDL-IC-stimulated LDLR expression. Electrophoretic mobility shift assays further demonstrated that LDL-ICs stimulated transcription factor AP-1 activity. Studies assessing the signaling pathways involved in LDLR up-regulation by LDL-ICs showed that the up-regulation of LDLR was extracellular signal-regulated kinase (ERK) dependent. In conclusion, the present study shows that LDL ICs up-regulate LDLR expression via the ERK signaling pathway and the AP-1 motif-dependent transcriptional activation.

L14 ANSWER 2 OF 13 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 1
ACCESSION NUMBER: 2003420685 EMBASE
TITLE: pp90(RSK)- and protein kinase C-dependent pathway regulates **p42/44(MAPK)**-induced **LDL receptor** transcription in HepG2 cells.
AUTHOR: Kapoor G.S.; Golden C.; Atkins B.; Mehta K.D.
CORPORATE SOURCE: K.D. Mehta, Dept. of Molec./Cell. Biochemistry, Ohio State University, Coll. of Medicine and Public Health, 1645 Neil Ave., Columbus, OH 43210, United States. mehta.80@osu.edu
SOURCE: Journal of Lipid Research, (2003) 44/3 (584-593).
Refs: 46
ISSN: 0022-2275 CODEN: JLPRAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB We have previously shown that different extracellular stimuli require

signaling through the Raf/MEK/**p42/ 44**(**MAPK**) cascade to induce **LDL receptor** expression. The present studies were designed to delineate the molecular mechanisms underlying **p42/44**(**MAPK**)-induced **LDL receptor** transcription in HepG2-ΔRaf-1:ER cells, a modified HepG2 cell line in which the Raf-1/MEK/**p42/44**(**MAPK**) cascade can be specifically activated by anti-estradiol ICI182,780 in an agonist-specific manner. Using these cells, we show that: a) **LDL receptor** induction was reduced in reporter constructs containing mutation in either Sp1 or sterol-regulatory element-1 (SRE-1) sites, whereas inactivation of both sites abolished the induction; b) E1A, which inhibits CREB binding protein (CBP), a common activator of SRE-1 binding protein and Sp1, strongly repressed the induction; c) intracellular inhibition of the 90 kDa ribosomal S6 kinase (pp90(RSK)) cascade reduced **LDL receptor** induction; d) highly selective protein kinase C (PKC) inhibitors effectively abrogated the induction without affecting activation of pp90 (RSK); and e) overexpression of PKCβ significantly induced **LDL receptor** promoter activity. Taken together, these results demonstrate that pp90(RSK) and PKCβ are downstream effectors and Sp1, SRE-1 binding protein, and CBP are part of the transcriptional complex resulting in induction of **LDL receptor** expression in response to activation of the Raf/MEK/**p42/44**(**MAPK**) cascade. These findings identify for the first time a role for PKCβ in determining the specificity of **p42/44**(**MAPK**) signaling by participating with pp90(RSK) in regulating gene expression.

L14 ANSWER 3 OF 13 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2002270304 MEDLINE
DOCUMENT NUMBER: 21993139 PubMed ID: 11997513
TITLE: Critical role of diacylglycerol- and phospholipid-regulated protein kinase C epsilon in induction of low-density lipoprotein receptor transcription in response to depletion of cholesterol.
AUTHOR: Mehta Kamal D; Radominska-Pandya Anna; Kapoor Gurpreet S; Dave Bhuvanesh; Atkins Brett A
CORPORATE SOURCE: Department of Molecular and Cellular Biochemistry, The Ohio State University College of Medicine, Columbus, Ohio 43210, USA.. mehta.80@osu.edu
CONTRACT NUMBER: DK56226 (NIDDK)
R01 HL67760 (NHLBI)
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2002 Jun) 22 (11) 3783-93. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020516
Last Updated on STN: 20020611
Entered Medline: 20020606

AB Induction of low-density lipoprotein (**LDL**) **receptor** transcription in response to depletion of cellular sterols in animal cells is well established. The intracellular signal or signals involved in regulating this process, however, remain unknown. Using a specific inhibitor of protein kinase C (PKC), calphostin C, we show the requirement of this kinase in the induction process in human hepatoma HepG2 cells. Overexpression of PKC epsilon, but not PKC alpha, -gamma, -delta, or -zeta was found to dramatically induce (approximately 18-fold) **LDL receptor** promoter activity. Interestingly, PKC epsilon-mediated induction was found to be sterol resistant. To further establish that PKC epsilon is involved in the sterol regulation of **LDL receptor** gene transcription, endogenous PKC epsilon was

specifically inhibited by transfection with antisense PKC epsilon phosphorothionate oligonucleotides. Antisense treatment decreased endogenous PKC epsilon protein levels and completely blocked induction of **LDL receptor** transcription following sterol depletion. PKC epsilon-induced **LDL receptor** transcription is independent of the extracellular signal-regulated kinase 1 and 2 (**p42/44(MAPK)**) cascade, because the MEK-1/2 inhibitor, PD98059 did not inhibit, even though it blocked **p42/44(MAPK)** activation. Finally, photoaffinity labeling studies showed an isoform-specific interaction between PKC epsilon and sterols, suggesting that sterols may directly modulate its function by hampering binding of activators. This was confirmed by PKC activity assays. Altogether, these results define a novel signaling pathway leading to induction of **LDL receptor** transcription following sterol depletion, and a model is proposed to account for a new function for PKC epsilon as part of a sterol-sensitive signal transduction pathway in hepatic cells.

L14 ANSWER 4 OF 13 EMBASE
on STN DUPLICATE 3

ACCESSION NUMBER: 2002274870 EMBASE
TITLE: Role of mitogen-activated protein kinases and protein kinase C in regulating low-density lipoprotein receptor expression.
AUTHOR: Mehta K.D.
CORPORATE SOURCE: K.D. Mehta, Department of Cellular Biochemistry, Ohio State Univ. College of Medicine, Columbus, OH 43210, United States. mehta.80@osu.edu
SOURCE: Gene Expression, (2002) 10/4 (153-164).
Refs: 95
ISSN: 1052-2166 CODEN: GEEXEJ
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The cell signaling pathways that culminate in induction of low-density lipoprotein (**LDL**) **receptor** transcription in response to a variety of extracellular and intracellular signals are beginning to be defined. Evidence is accumulating that **LDL receptor** transcription is under complex regulation and that a major pathway of induction by cytokines, growth factors, anisomycin, and phorbol esters involves the extracellular/mitogen-activated protein kinase (**p42/44(MAPK)**) cascade. In fact, degree **p42/44(MAPK)** activation determines the extent of **LDL receptor** induction. The suppression of **LDL receptor** expression by stress-activated p38(MAPK) via **p42/44(MAPK)** provides a potential mechanism for stress-induced hypercholesterolemia observed in humans and animals. Moreover, endogenous signals such as cholesterol regulate **LDL receptor** transcription through a different signaling cascade involving protein kinase Cε isoform (PKCε). The ability of cholesterol to directly bind PKCε in an isoform-specific manner strongly supports its role in sensing the cellular cholesterol levels. The emerging picture from the above studies is that regulation of **LDL receptor** transcription results from the activity of a number of interlinked regulatory molecules and pathways, rather than from a single linear series of events. These studies will provide the necessary framework for understanding differential responses within human populations to atherosclerosis following high-fat/cholesterol diet. This information may also provide new strategies to modulate specific gene expression with the hope to develop novel therapies for the treatment of hypercholesterolemia.

L14 ANSWER 5 OF 13 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:186246 BIOSIS
DOCUMENT NUMBER: PREV200300186246
TITLE: Requirement of pp90RSK and protein kinase C in p42/44MAPK-induced **LDL receptor** transcription.
AUTHOR(S): Mehta, K. D. [Reprint Author]; Atkins, B. [Reprint Author]; Kapoor, G. S. [Reprint Author]
CORPORATE SOURCE: Molecular and Cellular Biochemistry, College of Medicine, Ohio State University, Columbus, OH, USA
SOURCE: Molecular Biology of the Cell, (Nov 2002) Vol. 13, No. Supplement, pp. 17a. print.
Meeting Info.: 42nd Annual Meeting of the American Society for Cell Biology. San Francisco, CA, USA. December 14-18, 2002. American Society for Cell Biology.
ISSN: 1059-1524 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Apr 2003
Last Updated on STN: 16 Apr 2003

L14 ANSWER 6 OF 13 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2002433781 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12190111
TITLE: Activation of Raf-1/MEK-1/2/**p42/44**(**MAPK**) cascade alone is sufficient to uncouple **LDL receptor** expression from cell growth.
AUTHOR: Kapoor Gurpreet S; Atkins Brett A; Mehta Kamal D
CORPORATE SOURCE: Department of Molecular and Cellular Biochemistry, The Ohio State University College of Medicine, Columbus 43210, USA.
CONTRACT NUMBER: R01 HL-65540-01A1 (NHLBI)
SOURCE: Molecular and cellular biochemistry, (2002 Jul) 236 (1-2) 13-22.
Journal code: 0364456. ISSN: 0300-8177.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20020823
Last Updated on STN: 20030416
Entered Medline: 20030410

AB Our previous observation that induction of low density lipoprotein (**LDL**) **receptor** expression by a variety of extracellular signals is blocked by PD98059, a specific mitogen-activated protein kinase kinase inhibitor, led to the suggestion that the growth-responsive **p42/44**(**MAPK**) cascade plays a critical role in regulating **LDL receptor** transcription. To analyze the specific contribution of the **p42/44**(**MAPK**) cascade in regulating cell growth and **LDL receptor** induction, we established a HepG2-derived cell line that stably expresses an inducible form of oncogenic human Raf-1 kinase. Using this system, we provide direct evidence that specific activation of this cascade alone is not only required but is sufficient to fully induce **LDL receptor** expression. Interestingly, degree of **p42/44**(**MAPK**) activation determines the extent of **LDL receptor** induction. However, activation of **p42/44**(**MAPK**) in the above cells led to the inhibition of DNA synthesis, caused growth arrest, decrease in cyclin A and upregulation of p21(Cip) expression in a time-dependent manner. These results suggest that each of these two processes can be regulated independently of each other in response to **p42/44**(**MAPK**)

activation. Thus, extent of **p42/44(MAPK)** activation may be important in transducing divergent cellular responses in human cells with implications for altered signaling resulting in hypercholesterolemia.

L14 ANSWER 7 OF 13 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2000:559059 SCISEARCH
THE GENUINE ARTICLE: 313NH
TITLE: High intensity **p42/44(MAPK)** cascade uncouples **LDL receptor** induction from cell growth.
AUTHOR: Mehta K (Reprint); Kapoor G; Atkins B
CORPORATE SOURCE: UNIV ARKANSAS, COLL MED, LITTLE ROCK, AR 72205
COUNTRY OF AUTHOR: USA
SOURCE: FASEB JOURNAL, (11 MAY 2000) Vol. 14, No. 8, pp. 308-308. Publisher: FEDERATION AMER SOC EXP BIOL, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 0

L14 ANSWER 8 OF 13 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2000226341 EMBASE
TITLE: Inhibition of stress-activated p38 mitogen-activated protein kinase induces low-density lipoprotein receptor expression.
AUTHOR: Mehta K.D.; Miller L.
CORPORATE SOURCE: K.D. Mehta, Dept. Biochemistry/Molecular Biology, College of Medicine, University of Arkansas, 4301 West Markham, Little Rock, AR 72205, United States
SOURCE: Trends in Cardiovascular Medicine, (2000) 9/7 (201-205). Refs: 38
ISSN: 1050-1738 CODEN: TCMDEQ
PUBLISHER IDENT.: S 1050-1738(00)00021-9
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
025 Hematology
029 Clinical Biochemistry
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We have recently shown that different signal transduction pathways initiated by a variety of agents converge on growth-responsive **p42/44(MAPK)** signaling cascade to induce low-density lipoprotein (**LDL**) **receptor** expression. Our recent demonstration that stress-activated p38(MAPK) negatively regulates **LDL receptor** expression in an isoform-specific manner via modulation of **p42/44(MAPK)** cascade represents a new dimension of complexity in the molecular communication that governs **LDL receptor** expression. The suggested one-way communication between p38(MAPK) and **p42/44(MAPK)** provides a potential mechanism for fine-tuning cellular levels of cholesterol in response to a diverse set of environmental cues, including stress. Cross talk between MAPKs opens new avenues toward understanding a variety of pathogenic processes; this makes them tempting targets for therapeutic interventions in cardiovascular diseases.

L14 ANSWER 9 OF 13 MEDLINE on STN DUPLICATE 5

ACCESSION NUMBER: 1999321880 MEDLINE
DOCUMENT NUMBER: 99321880 PubMed ID: 10391894
TITLE: One-way cross-talk between p38(MAPK) and **p42/44(MAPK)**. Inhibition of p38(MAPK) induces low density lipoprotein receptor expression through activation of the **p42/44(MAPK)** cascade.
AUTHOR: Singh R P; Dhawan P; Golden C; Kapoor G S; Mehta K D
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205, USA.
CONTRACT NUMBER: HL-51592 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Jul 9) 274 (28) 19593-600.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990816
Last Updated on STN: 20000303
Entered Medline: 19990805

AB In this paper, we report that SB202190 alone, a specific inhibitor of p38(MAPK), induces low density lipoprotein (**LDL**) **receptor** expression (6-8-fold) in a sterol-sensitive manner in HepG2 cells. Consistent with this finding, selective activation of the p38(MAPK) signaling pathway by expression of MKK6b(E), a constitutive activator of p38(MAPK), significantly reduced **LDL receptor** promoter activity. Expression of the p38(MAPK) alpha-isoform had a similar effect, whereas expression of the p38(MAPK) betaII-isoform had no significant effect on **LDL receptor** promoter activity. SB202190-dependent increase in **LDL receptor** expression was accompanied by induction of **p42/44(MAPK)**, and inhibition of this pathway completely prevented SB202190-induced **LDL receptor** expression, suggesting that p38(MAPK) negatively regulates the **p42/44(MAPK)** cascade and the responses mediated by this kinase. Cross-talk between these kinases appears to be one-way because modulation of **p42/44(MAPK)** activity did not affect p38(MAPK) activation by a variety of stress inducers. Taken together, these findings reveal a hitherto unrecognized one-way communication that exists between p38(MAPK) and **p42/44(MAPK)** and provide the first evidence that through the **p42/44(MAPK)** signaling cascade, the p38(MAPK) alpha-isoform negatively regulates **LDL receptor** expression, thus representing a novel mechanism of fine tuning cellular levels of cholesterol in response to a diverse set of environmental cues.

L14 ANSWER 10 OF 13 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 1999438160 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10508211
TITLE: Critical role of **p42/44(MAPK)** activation in anisomycin and hepatocyte growth factor-induced **LDL receptor** expression: activation of Raf-1/Mek-1/**p42/44(MAPK)** cascade alone is sufficient to induce **LDL receptor** expression.
AUTHOR: Dhawan P; Bell A; Kumar A; Golden C; Mehta K D
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, College of Medicine, University of Arkansas for Medical Sciences, 4301 West Markham, Little Rock, AR 72205, USA.
CONTRACT NUMBER: HL-51592-04 (NHLBI)
SOURCE: Journal of lipid research, (1999 Oct) 40 (10) 1911-9.

Journal code: 0376606. ISSN: 0022-2275.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20020420
Entered Medline: 19991223

AB The protein synthesis inhibitor anisomycin activates stress-related mitogen-activated protein kinases (MAPKs), namely, c-jun NH(2)-terminal kinase (p46/54(JNK)) and p38(MAPK) in mammalian cells. In this paper, we show that although exposure to anisomycin resulted in rapid and strong activation of p46/54(JNK) and p38(MAPK), with a delayed low level dual-phosphorylation of mitogen/extracellular protein kinase (**p42/44(MAPK)**), low density lipoprotein (**LDL**) **receptor** induction depends solely on the mild activation of **p42/44(MAPK)** signaling cascade in HepG2 cells. Unlike hepatocyte growth factor (HGF) which caused **LDL receptor** induction via rapid, strong, and Ras-dependent **p42/44(MAPK)** activation, anisomycin-induced **p42/44(MAPK)** activity and increased **LDL receptor** expression in a Ras-independent manner. Finally, we examined the role of the **p42/44(MAPK)** signaling cascade in **LDL receptor** induction by activating this kinase independently of anisomycin or HGF. By using estrogen-dependent human Raf-1 protein kinase in transient transfection assays, we show that the exclusive activation of the Raf-1/MEK-1/**p42/44(MAPK)** signaling cascade with antiestrogen ICI 182, 780 caused induction of **LDL receptor** expression to the same level as observed with either HGF or anisomycin. Consistent with the role of **p42/44(MAPK)**, induction was strongly inhibited by pretreatment with the MEK-1/2 inhibitor PD98059.Our observation that anisomycin can use **p42/44(MAPK)** signaling cascade is a departure from established thinking, and the results presented shows that activation of the **p42/44(MAPK)** alone is sufficient to fully induce **LDL receptor** transcription.

L14 ANSWER 11 OF 13 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2000:468792 SCISEARCH
THE GENUINE ARTICLE: 325ZV
TITLE: Inhibition of stress-activated p38 mitogen-activated protein kinase induces low-density lipoprotein receptor expression
AUTHOR: Mehta K D (Reprint); Miller L
CORPORATE SOURCE: UNIV ARKANSAS MED SCI, COLL MED, DEPT BIOCHEM & MOL BIOL, SLOT 516, 4301 W MARKHAM, LITTLE ROCK, AR 72205 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: TRENDS IN CARDIOVASCULAR MEDICINE, (OCT 1999) Vol. 9, No. 7, pp. 201-205.
Publisher: ELSEVIER SCIENCE LONDON, 84 THEOBALDS RD, LONDON WC1X 8RR, ENGLAND.
ISSN: 1050-1738.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 38

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We have recently shown that different signal transduction. pathways initiated by a variety of agents converge on growth-responsive **p42/44(MAPK)** signaling cascade to induce low-density lipoprotein (**LDL**) **receptor** expression. Our recent demonstration that stress-activated p38(MAPK) negatively regulates

LDL receptor expression in an isoform-specific manner via modulation of **p42/44(MAPK)** cascade represents a view dimension of complexity in. the molecular communication that governs **LDL receptor** expression. The suggested one-way communication between p38(MAPK) and **p42/44(MAPK)** provides a potential mechanism for fine-tuning cellular levels of cholesterol in response to a diverse set of environmental cues, including stress. Cross talk between MAPKs opens new avenues toward understanding a variety of pathogenic processes; this makes them tempting targets for therapeutic interventions in cardiovascular diseases. (Trends Cardiovasc Med 1999;9:201-205), (C) 1999, Elsevier Science Inc.

L14 ANSWER 12 OF 13 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1999:167257 BIOSIS
DOCUMENT NUMBER: PREV199900167257
TITLE: **LDL receptor** expression is regulated positively by P42/44MAPK pathway in hepatic cells.
AUTHOR(S): Dhawan, P. [Reprint author]; McMahon, M.; Mehta, K. D. [Reprint author]
CORPORATE SOURCE: Dep. Biochemistry Molecular Biology, Univ. Ark. Med. Sciencdes 4301, West Markham St., Littlerock, AR 72205, USA
SOURCE: FASEB Journal, (March 12, 1999) Vol. 13, No. 4 PART 1, pp. A194. print.
Meeting Info.: Annual Meeting of the Professional Research Scientists for Experimental Biology 99. Washington, D.C., USA. April 17-21, 1999.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Apr 1999
Last Updated on STN: 19 Apr 1999

L14 ANSWER 13 OF 13 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 1999:808341 SCISEARCH
THE GENUINE ARTICLE: 226QW
TITLE: **Ldl receptor** expression is regulated positively by **p42/44(MAPK)** pathway in hepatic cells.
AUTHOR: Dhawan P (Reprint); McMahon M; Mehta K D
CORPORATE SOURCE: UNIV ARKANSAS MED SCI, DEPT BIOCHEM & MOL BIOL, LITTLE ROCK, AR 72205; UNIV CALIF SAN FRANCISCO, CANC RES INST, SAN FRANCISCO, CA 94145
COUNTRY OF AUTHOR: USA
SOURCE: FASEB JOURNAL, (12 MAR 1999) Vol. 13, No. 4, Part 1, Supp. [S], pp. A194-A194.
Publisher: FEDERATION AMER SOC EXP BIOL, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998.
ISSN: 0892-6638.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 0

=> e mehta k d/au
E1 17 MEHTA K B/AU
E2 104 MEHTA K C/AU
E3 128 --> MEHTA K D/AU
E4 16 MEHTA K G/AU
E5 8 MEHTA K H/AU
E6 6 MEHTA K I/AU
E7 29 MEHTA K J/AU
E8 58 MEHTA K K/AU

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E9          60      MEHTA K M/AU
E10         62      MEHTA K N/AU
E11         97      MEHTA K P/AU
E12         24      MEHTA K R/AU

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L15        128 "MEHTA K D"/AU

=> d his

     (FILE 'HOME' ENTERED AT 11:42:47 ON 13 FEB 2004)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 11:43:06 ON 13 FEB 2004
L1         23212 S "LDL RECEPTOR"
L2            14 S "LOW(A)DENSITY"
L3        237773 S LOW (A)DENSITY
L4        424929 S LIPOPROTEIN?
L5       3623226 S RECEPTOR?
L6         26576 S L4(A)L5
L7         18188 S L3(A)L6
L8           941 S "P42/44 MAPK"
L9            16 S L7 AND L8
L10            9 DUP REM L9 (7 DUPLICATES REMOVED)
L11           16 S L8 AND L6
L12            9 DUP REM L11 (7 DUPLICATES REMOVED)
L13           25 S L1 AND L8
L14           13 DUP REM L13 (12 DUPLICATES REMOVED)
                 E MEHTA K D/AU
L15          128 S E3

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L16       32841 L1 OR L7

=> s l15 and l16
L17          60 L15 AND L16

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ENTER L# LIST OR (END):end

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PROCESSING COMPLETED FOR L17
L18           21 DUP REM L17 (39 DUPLICATES REMOVED)

=> d 1-21 ibib ab

L18  ANSWER 1 OF 21  EMBASE  COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
     on STN                                              DUPLICATE 1
ACCESSION NUMBER:   2003420685  EMBASE
TITLE:              pp90(RSK)- and protein kinase C-dependent pathway regulates
                    p42/44(MAPK)-induced LDL receptor
                    transcription in HepG2 cells.
AUTHOR:             Kapoor G.S.; Golden C.; Atkins B.; Mehta K.D.
CORPORATE SOURCE:   K.D. Mehta, Dept. of Molec./Cell. Biochemistry, Ohio State
                    University, Coll. of Medicine and Public Health, 1645 Neil
                    Ave., Columbus, OH 43210, United States. mehta.80@osu.edu
SOURCE:             Journal of Lipid Research, (2003) 44/3 (584-593).
                    Refs: 46
                    ISSN: 0022-2275  CODEN: JLPRAW
COUNTRY:            United States
DOCUMENT TYPE:      Journal; Article
FILE SEGMENT:       018     Cardiovascular Diseases and Cardiovascular Surgery
                    029     Clinical Biochemistry
LANGUAGE:           English
```

SUMMARY LANGUAGE: English

AB We have previously shown that different extracellular stimuli require signaling through the Raf/MEK/p42/ 44(MAPK) cascade to induce **LDL receptor** expression. The present studies were designed to delineate the molecular mechanisms underlying p42/44(MAPK)-induced **LDL receptor** transcription in HepG2-ΔRaf-1:ER cells, a modified HepG2 cell line in which the Raf-1/MEK/p42/44(MAPK) cascade can be specifically activated by anti-estradiol ICI182,780 in an agonist-specific manner. Using these cells, we show that: a) **LDL receptor** induction was reduced in reporter constructs containing mutation in either Sp1 or sterol-regulatory element-1 (SRE-1) sites, whereas inactivation of both sites abolished the induction; b) E1A, which inhibits CREB binding protein (CBP), a common activator of SRE-1 binding protein and Sp1, strongly repressed the induction; c) intracellular inhibition of the 90 kDa ribosomal S6 kinase (pp90(RSK)) cascade reduced **LDL receptor** induction; d) highly selective protein kinase C (PKC) inhibitors effectively abrogated the induction without affecting activation of pp90 (RSK); and e) overexpression of PKCβ significantly induced **LDL receptor** promoter activity. Taken together, these results demonstrate that pp90(RSK) and PKCβ are downstream effectors and Sp1, SRE-1 binding protein, and CBP are part of the transcriptional complex resulting in induction of **LDL receptor** expression in response to activation of the Raf/MEK/p42/44(MAPK) cascade. These findings identify for the first time a role for PKCβ in determining the specificity of p42/44 (MAPK) signaling by participating with pp90(RSK) in regulating gene expression.

L18 ANSWER 2 OF 21 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 2

ACCESSION NUMBER: 2002179351 EMBASE

TITLE: Critical role of diacylglycerol- and phospholipid-regulated protein kinase Cε in Induction of **low-density lipoprotein receptor** transcription in response to depletion of cholesterol.

AUTHOR: **Mehta K.D.**; Radominska-Pandya A.; Kapoor G.S.; Dave B.; Atkins B.A.

CORPORATE SOURCE: K.D. Mehta, Department of Cellular Biochemistry, Ohio State Univ. College of Medicine, 464 Hamilton Hall, 1645 Neil Ave., Columbus, OH 43210, United States. mehta.80@osu.edu

SOURCE: Molecular and Cellular Biology, (2002) 22/11 (3783-3793). Refs: 58
ISSN: 0270-7306 CODEN: MCEBD4

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Induction of low-density lipoprotein (**LDL**) **receptor** transcription in response to depletion of cellular sterols in animal cells is well established. The intracellular signal or signals involved in regulating this process, however, remain unknown. Using a specific inhibitor of protein kinase C (PKC), calphostin C, we show the requirement of this kinase in the induction process in human hepatoma HepG2 cells. Overexpression of PKCε, but not PKCα, -γ, -δ, or ζ was found to dramatically induce (approximately 18-fold) **LDL receptor** promoter activity. Interestingly, PKCε-mediated induction was found to be sterol resistant. To further establish that PKCε is involved in the sterol regulation of **LDL receptor** gene transcription, endogenous PKCε was specifically inhibited by transfection with antisense PKCε phosphorothionate oligonucleotides. Antisense treatment decreased endogenous PKCε protein levels and completely blocked induction of **LDL receptor** transcription following sterol depletion. PKCε-induced **LDL receptor**

transcription is independent of the extracellular signal-regulated kinase 1 and 2 (p42/44(MAPK)) cascade, because the MEK-1/2 inhibitor, PD98059 did not inhibit, even though it blocked p42/44(MAPK) activation. Finally, photoaffinity labeling studies showed an isoform-specific interaction between PKCε and sterols, suggesting that sterols may directly modulate its function by hampering binding of activators. This was confirmed by PKC activity assays. Altogether, these results define a novel signaling pathway leading to induction of **LDL receptor** transcription following sterol depletion, and a model is proposed to account for a new function for PKCε as part of a sterol-sensitive signal transduction pathway in hepatic cells.

L18 ANSWER 3 OF 21 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 3

ACCESSION NUMBER: 2002274870 EMBASE
TITLE: Role of mitogen-activated protein kinases and protein kinase C in regulating **low-density lipoprotein receptor** expression.
AUTHOR: **Mehta K.D.**
CORPORATE SOURCE: K.D. Mehta, Department of Cellular Biochemistry, Ohio State Univ. College of Medicine, Columbus, OH 43210, United States. mehta.80@osu.edu
SOURCE: Gene Expression, (2002) 10/4 (153-164).
Refs: 95
ISSN: 1052-2166 CODEN: GEEXEJ
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The cell signaling pathways that culminate in induction of low-density lipoprotein (**LDL**) **receptor** transcription in response to a variety of extracellular and intracellular signals are beginning to be defined. Evidence is accumulating that **LDL receptor** transcription is under complex regulation and that a major pathway of induction by cytokines, growth factors, anisomycin, and phorbol esters involves the extracellular/mitogen-activated protein kinase (p42/44(MAPK)) cascade. In fact, degree p42/44(MAPK) activation determines the extent of **LDL receptor** induction. The suppression of **LDL receptor** expression by stress-activated p38(MAPK) via p42/44(MAPK) provides a potential mechanism for stress-induced hypercholesterolemia observed in humans and animals. Moreover, endogenous signals such as cholesterol regulate **LDL receptor** transcription through a different signaling cascade involving protein kinase Cε isoform (PKCε). The ability of cholesterol to directly bind PKCε in an isoform-specific manner strongly supports its role in sensing the cellular cholesterol levels. The emerging picture from the above studies is that regulation of **LDL receptor** transcription results from the activity of a number of interlinked regulatory molecules and pathways, rather than from a single linear series of events. These studies will provide the necessary framework for understanding differential responses within human populations to atherosclerosis following high-fat/cholesterol diet. This information may also provide new strategies to modulate specific gene expression with the hope to develop novel therapies for the treatment of hypercholesterolemia.

L18 ANSWER 4 OF 21 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 4

ACCESSION NUMBER: 2003:186246 BIOSIS
DOCUMENT NUMBER: PREV200300186246
TITLE: Requirement of pp90RSK and protein kinase C in p42/44MAPK-induced **LDL receptor** transcription.
AUTHOR(S): **Mehta, K. D.** [Reprint Author]; Atkins, B.

[Reprint Author]; Kapoor, G. S. [Reprint Author]
CORPORATE SOURCE: Molecular and Cellular Biochemistry, College of Medicine, Ohio State University, Columbus, OH, USA
SOURCE: Molecular Biology of the Cell, (Nov 2002) Vol. 13, No. Supplement, pp. 17a. print.
Meeting Info.: 42nd Annual Meeting of the American Society for Cell Biology. San Francisco, CA, USA. December 14-18, 2002. American Society for Cell Biology.
ISSN: 1059-1524 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Apr 2003
Last Updated on STN: 16 Apr 2003

L18 ANSWER 5 OF 21 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 5
ACCESSION NUMBER: 2002279144 EMBASE
TITLE: Activation of Raf-1/MEK-1/2/p42/44(MAPK) cascade alone is sufficient to uncouple **LDL receptor** expression from cell growth.
AUTHOR: Kapoor G.S.; Atkins B.A.; **Mehta K.D.**
CORPORATE SOURCE: K.D. Mehta, Dept. of Molecular/Cell. Biochemist., Ohio State Univ. College Medicine, 464 Hamilton Hall, 1645 Neil Avenue, Columbus, OH 43210, United States. mehta.80@osu.edu
SOURCE: Molecular and Cellular Biochemistry, (2002) 236/1-2 (13-22).
Refs: 36
ISSN: 0300-8177 CODEN: MCBIB8
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Our previous observation that induction of low density lipoprotein (**LDL**) **receptor** expression by a variety of extracellular signals is blocked by PD98059, a specific mitogen-activated protein kinase kinase inhibitor, led to the suggestion that the growth-responsive p42/44(MAPK) cascade plays a critical role in regulating **LDL receptor** transcription. To analyze the specific contribution of the p42/44(MAPK) cascade in regulating cell growth and **LDL receptor** induction, we established a HepG2-derived cell line that stably expresses an inducible form of oncogenic human Raf-1 kinase. Using this system, we provide direct evidence that specific activation of this cascade alone is not only required but is sufficient to fully induce **LDL receptor** expression. Interestingly, degree of p42/44(MAPK) activation determines the extent of **LDL receptor** induction. However, activation of p42/44(MAPK) in the above cells led to the inhibition of DNA synthesis, caused growth arrest, decrease in cyclin A and upregulation of p21(Cip) expression in a time-dependent manner. These results suggest that each of these two processes can be regulated independently of each other in response to p42/44(MAPK) activation. Thus, extent of p42/44(MAPK) activation may be important in transducing divergent cellular responses in human cells with implications for altered signaling resulting in hypercholesterolemia.

L18 ANSWER 6 OF 21 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2000226341 EMBASE
TITLE: Inhibition of stress-activated p38 mitogen-activated protein kinase induces **low-density lipoprotein receptor** expression.
AUTHOR: **Mehta K.D.**; Miller L.

CORPORATE SOURCE: K.D. Mehta, Dept. Biochemistry/Molecular Biology, College of Medicine, University of Arkansas, 4301 West Markham, Little Rock, AR 72205, United States
SOURCE: Trends in Cardiovascular Medicine, (2000) 9/7 (201-205). Refs: 38
ISSN: 1050-1738 CODEN: TCMDEQ
PUBLISHER IDENT.: S 1050-1738(00)00021-9
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
025 Hematology
029 Clinical Biochemistry
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We have recently shown that different signal transduction pathways initiated by a variety of agents converge on growth-responsive p42/44(MAPK) signaling cascade to induce low-density lipoprotein (**LDL**) **receptor** expression. Our recent demonstration that stress-activated p38(MAPK) negatively regulates **LDL receptor** expression in an isoform-specific manner via modulation of p42/44(MAPK) cascade represents a new dimension of complexity in the molecular communication that governs **LDL receptor** expression. The suggested one-way communication between p38(MAPK) and p42/44(MAPK) provides a potential mechanism for fine-tuning cellular levels of cholesterol in response to a diverse set of environmental cues, including stress. Cross talk between MAPKs opens new avenues toward understanding a variety of pathogenic processes; this makes them tempting targets for therapeutic interventions in cardiovascular diseases.

L18 ANSWER 7 OF 21 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 6
ACCESSION NUMBER: 1999:173132 BIOSIS
DOCUMENT NUMBER: PREV199900173132
TITLE: Cis-acting element in the human **LDL receptor** promoter and uses thereof.
AUTHOR(S): **Mehta, K. D.** [Inventor]
CORPORATE SOURCE: Little Rock, Ark., USA
ASSIGNEE: THE UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES
PATENT INFORMATION: US 5879879 March 9, 1999
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (March 9, 1999) Vol. 1220, No. 2, pp. 1492. print.
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 5 May 1999
Last Updated on STN: 5 May 1999

L18 ANSWER 8 OF 21 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 1999321880 MEDLINE
DOCUMENT NUMBER: 99321880 PubMed ID: 10391894
TITLE: One-way cross-talk between p38(MAPK) and p42/44(MAPK). Inhibition of p38(MAPK) induces **low density lipoprotein receptor** expression through activation of the p42/44(MAPK) cascade.
AUTHOR: Singh R P; Dhawan P; Golden C; Kapoor G S; **Mehta K D**
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205, USA.
CONTRACT NUMBER: HL-51592 (NHLBI)

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Jul 9) 274 (28) 19593-600.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990816
Last Updated on STN: 20000303
Entered Medline: 19990805

AB In this paper, we report that SB202190 alone, a specific inhibitor of p38(MAPK), induces low density lipoprotein (**LDL**) **receptor** expression (6-8-fold) in a sterol-sensitive manner in HepG2 cells. Consistent with this finding, selective activation of the p38(MAPK) signaling pathway by expression of MKK6b(E), a constitutive activator of p38(MAPK), significantly reduced **LDL** **receptor** promoter activity. Expression of the p38(MAPK) alpha-isoform had a similar effect, whereas expression of the p38(MAPK) betaII-isoform had no significant effect on **LDL receptor** promoter activity. SB202190-dependent increase in **LDL** **receptor** expression was accompanied by induction of p42/44(MAPK), and inhibition of this pathway completely prevented SB202190-induced **LDL receptor** expression, suggesting that p38(MAPK) negatively regulates the p42/44(MAPK) cascade and the responses mediated by this kinase. Cross-talk between these kinases appears to be one-way because modulation of p42/44(MAPK) activity did not affect p38(MAPK) activation by a variety of stress inducers. Taken together, these findings reveal a hitherto unrecognized one-way communication that exists between p38(MAPK) and p42/44(MAPK) and provide the first evidence that through the p42/44(MAPK) signaling cascade, the p38(MAPK) alpha-isoform negatively regulates **LDL receptor** expression, thus representing a novel mechanism of fine tuning cellular levels of cholesterol in response to a diverse set of environmental cues.

L18 ANSWER 9 OF 21 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 1999438160 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10508211
TITLE: Critical role of p42/44(MAPK) activation in anisomycin and hepatocyte growth factor-induced **LDL** **receptor** expression: activation of Raf-1/Mek-1/p42/44(MAPK) cascade alone is sufficient to induce **LDL receptor** expression.
AUTHOR: Dhawan P; Bell A; Kumar A; Golden C; **Mehta K D**
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, College of Medicine, University of Arkansas for Medical Sciences, 4301 West Markham, Little Rock, AR 72205, USA.
CONTRACT NUMBER: HL-51592-04 (NHLBI)
SOURCE: Journal of lipid research, (1999 Oct) 40 (10) 1911-9.
Journal code: 0376606. ISSN: 0022-2275.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20020420
Entered Medline: 19991223

AB The protein synthesis inhibitor anisomycin activates stress-related mitogen-activated protein kinases (MAPKs), namely, c-jun NH(2)-terminal kinase (p46/54(JNK)) and p38(MAPK) in mammalian cells. In this paper, we show that although exposure to anisomycin resulted in rapid and strong activation of p46/54(JNK) and p38(MAPK), with a delayed low level dual-phosphorylation of mitogen/extracellular protein kinase

(p42/44(MAPK)), low density lipoprotein (**LDL**) **receptor** induction depends solely on the mild activation of p42/44(MAPK) signaling cascade in HepG2 cells. Unlike hepatocyte growth factor (HGF) which caused **LDL receptor** induction via rapid, strong, and Ras-dependent p42/44(MAPK) activation, anisomycin-induced p42/44(MAPK) activity and increased **LDL receptor** expression in a Ras-independent manner. Finally, we examined the role of the p42/44(MAPK) signaling cascade in **LDL receptor** induction by activating this kinase independently of anisomycin or HGF. By using estrogen-dependent human Raf-1 protein kinase in transient transfection assays, we show that the exclusive activation of the Raf-1/MEK-1/p42/44(MAPK) signaling cascade with antiestrogen ICI 182, 780 caused induction of **LDL receptor** expression to the same level as observed with either HGF or anisomycin. Consistent with the role of p42/44(MAPK), induction was strongly inhibited by pretreatment with the MEK-1/2 inhibitor PD98059.Our observation that anisomycin can use p42/44(MAPK) signaling cascade is a departure from established thinking, and the results presented shows that activation of the p42/44(MAPK) alone is sufficient to fully induce **LDL receptor** transcription.

L18 ANSWER 10 OF 21 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 2000385963 MEDLINE
DOCUMENT NUMBER: 20338661 PubMed ID: 10881752
TITLE: Inhibition of stress-activated p38 mitogen-activated protein kinase induces **low-density lipoprotein receptor** expression.
AUTHOR: **Mehta K D**; Miller L
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock 72205, USA.
SOURCE: TRENDS IN CARDIOVASCULAR MEDICINE, (1999 Oct) 9 (7) 201-5. Ref: 38
Journal code: 9108337. ISSN: 1050-1738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000818
Last Updated on STN: 20000818
Entered Medline: 20000809

AB We have recently shown that different signal transduction pathways initiated by a variety of agents converge on growth-responsive p42/44MAPK signaling cascade to induce low-density lipoprotein (**LDL**) **receptor** expression. Our recent demonstration that stress-activated p38MAPK negatively regulates **LDL receptor** expression in an isoform-specific manner via modulation of p42/44MAPK cascade represents a new dimension of complexity in the molecular communication that governs **LDL receptor** expression. The suggested one-way communication between p38MAPK and p42/44MAPK provides a potential mechanism for fine-tuning cellular levels of cholesterol in response to a diverse set of environmental cues, including stress. Cross talk between MAPKs opens new avenues toward understanding a variety of pathogenic processes; this makes them tempting targets for therapeutic interventions in cardiovascular diseases.

L18 ANSWER 11 OF 21 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1999:167257 BIOSIS
DOCUMENT NUMBER: PREV199900167257
TITLE: **LDL receptor** expression is regulated positively by P42/44MAPK pathway in hepatic cells.

AUTHOR(S): Dhawan, P. [Reprint author]; McMahon, M.; **Mehta, K. D.** [Reprint author]
CORPORATE SOURCE: Dep. Biochemistry Molecular Biology, Univ. Ark. Med. Sciencdes 4301, West Markham St., Littlerock, AR 72205, USA
SOURCE: FASEB Journal, (March 12, 1999) Vol. 13, No. 4 PART 1, pp. A194. print.
Meeting Info.: Annual Meeting of the Professional Research Scientists for Experimental Biology 99. Washington, D.C., USA. April 17-21, 1999.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Apr 1999
Last Updated on STN: 19 Apr 1999

L18 ANSWER 12 OF 21 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 1999:808341 SCISEARCH
THE GENUINE ARTICLE: 226QW
TITLE: **Ldl receptor** expression is regulated positively by p42/44(MAPK) pathway in hepatic cells.
AUTHOR: Dhawan P (Reprint); McMahon M; **Mehta K D**
CORPORATE SOURCE: UNIV ARKANSAS MED SCI, DEPT BIOCHEM & MOL BIOL, LITTLE ROCK, AR 72205; UNIV CALIF SAN FRANCISCO, CANC RES INST, SAN FRANCISCO, CA 94145
COUNTRY OF AUTHOR: USA
SOURCE: FASEB JOURNAL, (12 MAR 1999) Vol. 13, No. 4, Part 1, Supp. [S], pp. A194-A194.
Publisher: FEDERATION AMER SOC EXP BIOL, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998.
ISSN: 0892-6638.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 0

L18 ANSWER 13 OF 21 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 1998288318 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9624172
TITLE: Differential roles of extracellular signal-regulated kinase-1/2 and p38(MAPK) in interleukin-1beta- and tumor necrosis factor-alpha-induced **low density lipoprotein receptor** expression in HepG2 cells.
AUTHOR: Kumar A; Middleton A; Chambers T C; **Mehta K D**
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205, USA.
CONTRACT NUMBER: HL-51592-04 (NHLBI)
SOURCE: Journal of biological chemistry, (1998 Jun 19) 273 (25) 15742-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980716
Last Updated on STN: 20000303
Entered Medline: 19980709
AB The inflammatory cytokines interleukin-1beta (IL-1beta) and tumor necrosis factor-alpha (TNF), elevated in inflammatory, malignant, and infectious diseases, induce low density lipoprotein (**LDL**) **receptor** transcription in HepG2 cells, and such an induction can account for

hypocholesterolemia associated with these states. However, the signaling mechanisms of cytokine-mediated **LDL receptor** induction are largely unexplored. In the present studies, we examined the potential involvement of different mitogen-activated protein kinase (MAPK) pathways. Northern analysis demonstrated that IL-1beta or TNF significantly increased **LDL receptor** transcript in HepG2 cells, whereas expression of another tightly regulated sterol-responsive squalene synthase gene was unaffected. IL-1beta treatment resulted in transient activation of three MAPK cascades, namely p46/54(JNK), p38(MAPK), and ERK-1/2, with maximal activation of 20-, 25-, and 3-fold, respectively, occurring 15-30 min after cytokine addition. PD98059, a specific inhibitor of MAPK kinase activity, inhibited IL-1beta-induced **LDL receptor** expression. In contrast, SB202190, a specific inhibitor of p38(MAPK), enhanced IL-1beta-induced **LDL receptor** expression, with a concomitant increase in ERK-1/2 activity. Similarly, TNF induced **LDL receptor** expression also required ERK-1/2 activation. Finally, sterols repressed IL-1beta induced receptor expression, without affecting ERK-1/2 activation. These results show that IL-1beta- or TNF-induced **LDL receptor** expression requires ERK-1/2 activation, that the p38(MAPK) pathway negatively regulates **LDL receptor** expression, and that sterols inhibit induction at a point downstream of ERK-1/2 in HepG2 cells.

L18 ANSWER 14 OF 21 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 97465961 MEDLINE
DOCUMENT NUMBER: 97465961 PubMed ID: 9321669
TITLE: Identification of essential nucleotides of the FP1 element responsible for enhancement of **low density lipoprotein receptor** gene transcription.
AUTHOR: Dhawan P; Chang R; **Mehta K D**
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, College of Medicine, University of Arkansas for Medical Sciences, 4301 West Markham, Little Rock, AR 72205, USA.
CONTRACT NUMBER: HL51592-04 (NHLBI)
SOURCE: NUCLEIC ACIDS RESEARCH, (1997 Oct 15) 25 (20) 4132-8. Journal code: 0411011. ISSN: 0305-1048.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971202

AB Low density lipoprotein (**LDL**) **receptor** gene is regulated at the transcriptional level by the intracellular level of sterols in animal cells. We have recently identified a 20 bp long region (-145 to -126), designated Footprint 1 (FP1), participating in maximal expression of the human **LDL receptor** gene in the absence of sterols in HepG2 cells [Mehta, K. D., Chang, R., Underwood, J., Wise, J. and Kumar, A. (1996) J. Biol. Chem ., 271, 33616-33622]. To determine the minimal FP1 sequence and to define the critical nucleotides required for function, a series of single nucleotide substitutions were introduced in the FP1 region. Twenty-three independent mutations were analyzed by transfection into HepG2 cells. These studies localize the regulatory region to 14 bp and demonstrate the requirement for essential guanine nucleotides at positions -135 and -136 for FP1 function. Furthermore, transfection studies suggest that the FP1-dependent increase in reporter gene expression is possibly mediated through interaction with the sterol-regulatory element. UV cross-linking and Southwestern blot analysis identified FP1-binding factors of approximately 50 and 125 kDa, which we have denoted p50 and p125. Mutations of the critical guanine residues (-135/-136) decreased the

formation of the specific protein-DNA complex with the FP1 sequence and abolished its binding to the p125. We conclude that direct interaction of the p125 factor with these nucleotides of the FP1 element potentially contributes to FP1-dependent induction of **LDL receptor** gene expression.

L18 ANSWER 15 OF 21 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 1998052315 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9392422
TITLE: Phorbol ester-induced **low density lipoprotein receptor** gene expression in HepG2 cells involves protein kinase C-mediated p42/44 MAP kinase activation.
AUTHOR: Kumar A; Chambers T C; Cloud-Heflin B A; **Mehta K D**
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Arkansas for Medical Sciences, Little Rock 72205-7199, USA.
CONTRACT NUMBER: HL-51592-04 (NHLBI)
SOURCE: Journal of lipid research, (1997 Nov) 38 (11) 2240-8. Journal code: 0376606. ISSN: 0022-2275.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980217
Last Updated on STN: 20000303
Entered Medline: 19980130

AB The signaling pathway involved in low density lipoprotein (**LDL**) **receptor** gene expression induced by the phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA) was investigated in the human hepatoma HepG2 cell line. Treatment of HepG2 cells with 100 nM TPA resulted in an approximately 20-fold increase in **LDL receptor** mRNA level, as determined by RT-PCR, which peaked at 2-4 h of treatment and subsequently declined. The protein kinase C (PKC) inhibitors calphostin C and staurosporine prevented TPA-mediated **LDL receptor** mRNA induction. In contrast, TPA did not affect squalene synthase mRNA expression. Immunoblotting of cell extracts with isozyme-specific PKC antibodies revealed that HepG2 cells expressed PKC alpha, which was mainly cytosolic, and PKC beta, PK epsilon, and PKC zeta, all of which were present in both the cytosolic and particulate fractions. Treatment of HepG2 cells with 100 nM TPA resulted in translocation of cytosolic PKC alpha to the particulate fraction, with a maximum at 30 min-2 h of treatment, but was without effect on the subcellular distribution of the other isozymes. TPA treatment also led to activation of the mitogen-activated protein kinase (MAPK) ERK cascade. The specific MAPK pathway inhibitor PD98059 blocked TPA-induced ERK activation. Furthermore, pretreatment of cells with PD98059 inhibited TPA-induced **LDL receptor** mRNA induction. Moreover, pretreatment of cells with calphostin C inhibited TPA-mediated ERK activation and **LDL receptor** mRNA induction in a dose-dependent fashion. Based on a close kinetic correlation between PKC alpha translocation and ERK activation, and the effects of specific inhibitors, these findings suggest that translocation/activation of PKC alpha, and subsequent activation of the Raf-1/MEK/ERK MAPK cascade, represent key events in the transcriptional induction of **LDL receptor** gene by TPA in HepG2 cells.

L18 ANSWER 16 OF 21 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 97126008 MEDLINE
DOCUMENT NUMBER: 97126008 PubMed ID: 8969230
TITLE: Identification of a novel cis-acting element participating in maximal induction of the human **low density lipoprotein receptor**

gene transcription in response to low cellular cholesterol levels.

AUTHOR: **Mehta K D**; Chang R; Underwood J; Wise J; Kumar A

CORPORATE SOURCE: Department of Biochemistry, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205, USA.

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Dec 27) 271 (52) 33616-22.
Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199701

ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 19970219
Entered Medline: 19970128

AB In this paper, we present both in vivo and in vitro evidence for the presence of a novel cis-acting regulatory element that is required for maximal induction of the human low density lipoprotein (**LDL**) **receptor** gene following depletion of cellular sterols in HepG2 cells. First, in vivo dimethyl sulfate footprinting of the human **LDL receptor** promoter before and after transcriptional induction in HepG2 cells revealed protection from -145 to -126, 5'-GAGCTTCACGGGTTAAAAAG-3' (referred to as FP1 site). Second, transient transfections of HepG2 cells with promoter luciferase reporter constructs containing the FP1 site resulted in significant enhancement (approximately 375%) of reporter gene expression in response to low levels of sterols compared with parallel plasmid without the FP1 site. In addition, this response was markedly attenuated on nucleotide substitutions within the FP1 site. Third, by electrophoretic mobility shift assays, the FP1 sequence was found to bind protein(s) from HepG2 nuclear extracts in a sequence-specific manner. In vitro binding of the FP1 mutants paralleled the results obtained for their in vivo transcription. On the basis of competition profiles, the FP1-binding factor is different from the known transcription factors binding to the AT-rich CArG and GArC motifs. Furthermore, the FP1-binding protein is not specific to HepG2 cells because nuclear factor(s) with the same specificity was observed in nuclear extracts of non-hepatic HeLa cells. We conclude that transcriptional induction of the **LDL receptor** gene in response to sterol depletion is mediated, in part, by an highly conserved novel cis-acting element through the binding of specific nuclear protein(s).

L18 ANSWER 17 OF 21 MEDLINE on STN DUPLICATE 14

ACCESSION NUMBER: 96158953 MEDLINE

DOCUMENT NUMBER: 96158953 PubMed ID: 8579582

TITLE: In vivo role of the Sp1 site neighboring sterol-responsive element-1 in controlling **low-density lipoprotein receptor** gene expression.

AUTHOR: Chang R; Yang E; Chamblis D; Kumar A; Wise J; **Mehta K D**

CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Arkansas for Medical Sciences, College of Medicine, Little Rock 72205, USA.

CONTRACT NUMBER: HL51592 (NHLBI)

SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1996 Jan 26) 218 (3) 733-9.
Journal code: 0372516. ISSN: 0006-291X.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199603

ENTRY DATE: Entered STN: 19960321
Last Updated on STN: 19960321
Entered Medline: 19960312

AB The in vivo role of the crucial Sp1 site neighboring sterol-responsive element-1 (SRE-1) in controlling **LDL receptor** gene expression in the presence or absence of sterols was examined. For this purpose the Xenopus laevis system was utilized as there are two different genes for **LDL receptors** in frogs which differ in their promoter region in the Sp1-binding sequence of repeat 3 present immediately adjacent to SRE-1. DNase I footprinting of promoters of both receptors showed differences in the affinity of this Sp1 site to purified transcription factor Sp1. Transcript levels of both **LDL receptors** were measured in livers of frogs on normal and cholesterol-enriched diets. Basal levels and extent of repression of **LDL receptor** gene on sterol administration were found to be dependent on the nature of the Sp1 site of repeat 3 under in vivo conditions. We conclude that this Sp1 site acts as a constitutive positive transcriptional element that forms a part of the active transcription complex irrespective of cellular sterol levels.

L18 ANSWER 18 OF 21 MEDLINE on STN DUPLICATE 15
ACCESSION NUMBER: 97077311 MEDLINE
DOCUMENT NUMBER: 97077311 PubMed ID: 8919878
TITLE: Chiloscyllium plagiosum **low-density lipoprotein receptor**: evolutionary conservation of five different functional domains.
AUTHOR: **Mehta K D**; Chang R; Norman J
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Arkansas for Medical Sciences, Little Rock 72205, USA.
SOURCE: JOURNAL OF MOLECULAR EVOLUTION, (1996 Feb) 42 (2) 264-72. Journal code: 0360051. ISSN: 0022-2844.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-L36118
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19980206
Entered Medline: 19961231

AB All five functional domains of the low-density lipoprotein (**LDL**) **receptor** were assembled in their modern form more than 450 million years ago, as revealed from the cloning and sequencing of an **LDL receptor** cDNA from Chiloscyllium plagiosum (banded cat shark). The shark **LDL receptor** has the same overall architecture as the mammalian and amphibian counterparts. Each of the seven cysteine-rich repeats in the ligand binding domain resembles its counterpart in the human **LDL receptor** more than it does the other repeats in the shark receptor as suggested by the presence of unique "signature" sequences, indicating that these repeats had already acquired their independent structures by the time of shark development. Furthermore, amino acid sequences of the entire ligand binding domain of shark **LDL receptor** show 35% identity over a stretch of 294 residues with a Lymnaea stagnalis G-protein-linked receptor (LSGLR). The region of homology between these unrelated proteins includes conservation of most of the unique characteristics of the cysteine-rich repeats of **LDL receptor** at the expected positions in LSGLR. The results presented are consistent with the hypothesis that all seven repeats in the ligand binding domain of **LDL receptor** may have been lifted directly from an ancestral gene instead of being evolutionary duplications of a single repeat recruited by the primitive **LDL receptor** from another gene.

L18 ANSWER 19 OF 21 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 95:769330 SCISEARCH
THE GENUINE ARTICLE: TB480
TITLE: IN-VIVO FOOTPRINTING OF HUMAN **LDL RECEPTOR** GENE PROMOTER - IMPLICATION FOR STEROL REGULATION OF GENE-EXPRESSION
AUTHOR: **MEHTA K D (Reprint)**; CHANG R X
CORPORATE SOURCE: UNIV ARKANSAS, COLL MED, LITTLE ROCK, AR, 72204
COUNTRY OF AUTHOR: USA
SOURCE: CIRCULATION, (15 OCT 1995) Vol. 92, No. 8, Supp. S, pp. 1724.
ISSN: 0009-7322.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: No References

L18 ANSWER 20 OF 21 MEDLINE on STN DUPLICATE 16
ACCESSION NUMBER: 91244816 MEDLINE
DOCUMENT NUMBER: 91244816 PubMed ID: 1709932
TITLE: The **low density lipoprotein receptor** in Xenopus laevis. II. Feedback repression mediated by conserved sterol regulatory element.
AUTHOR: **Mehta K D**; Brown M S; Bilheimer D W; Goldstein J L
CORPORATE SOURCE: Department of Molecular Genetics, University of Texas, Southwestern Medical Center, Dallas 75235.
CONTRACT NUMBER: HL 20948 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1991 Jun 5) 266 (16) 10415-9.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-M62977; GENBANK-M62979; GENBANK-M63255; GENBANK-M64332; GENBANK-S69601; GENBANK-S69604; GENBANK-S69828; GENBANK-S69830; GENBANK-S78749; GENBANK-S78751
ENTRY MONTH: 199107
ENTRY DATE: Entered STN: 19910719
Last Updated on STN: 19970203
Entered Medline: 19910701

AB The 5'-flanking regions of the two low density lipoprotein (**LDL**) **receptor** genes in Xenopus laevis contain three repeat sequences that are virtually identical to the repeats that mediate sterol-regulated transcription of the human **LDL receptor** gene. Like their human counterparts, Xenopus repeats 1 and 3, but not repeat 2, bind the transcription factor Sp1 and thus probably function as positive transcription elements. Xenopus repeat 2, like human repeat 2, contains all of the nucleotides that are required for sterol regulation. Administration of sterols repressed Xenopus **LDL receptor** mRNA in cultured A6 kidney cells and in the liver of intact frogs. In frogs this repression was associated with a 2-fold increase in plasma LDL levels. Xenopus LDL contains a protein corresponding in size to human apoB-100, a ligand for the **LDL receptor**. We found no evidence that frog plasma contains B-48, nor did we observe a clear-cut protein corresponding to apoE. We conclude that the structural gene for the **LDL receptor** has been under sterol-mediated regulation at least since the time of amphibian development more than 350 million years ago.

L18 ANSWER 21 OF 21 MEDLINE on STN DUPLICATE 17
ACCESSION NUMBER: 91244815 MEDLINE

DOCUMENT NUMBER: 91244815 PubMed ID: 1709931
TITLE: The **low density lipoprotein receptor** in Xenopus laevis. I. Five domains that resemble the human receptor.
AUTHOR: **Mehta K D**; Chen W J; Goldstein J L; Brown M S
CORPORATE SOURCE: Department of Molecular Genetics, University of Texas Southwestern Medical Center, Dallas 75235.
CONTRACT NUMBER: HL 20948 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1991 Jun 5) 266 (16) 10406-14.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-M62976; GENBANK-M62978; GENBANK-M63255; GENBANK-M64332; GENBANK-S69601; GENBANK-S69604; GENBANK-S69828; GENBANK-S69830; GENBANK-S78749; GENBANK-S78751
ENTRY MONTH: 199107
ENTRY DATE: Entered STN: 19910719
Last Updated on STN: 19960129
Entered Medline: 19910701

AB All five functional domains of the low density lipoprotein (**LDL**) **receptor** were assembled in their modern form more than 350 million years ago, as revealed from the sequence of two cloned cDNAs from the frog Xenopus laevis. The two cDNAs appear to represent duplicated copies of the **LDL receptor** gene that arose when the entire genome of Xenopus duplicated approximately 30 million years ago. Both frog **LDL receptors** bound Xenopus LDL with high affinity and human LDL with lower affinity when expressed in monkey COS cells. The receptors also showed high affinity for rabbit beta-migrating very low density lipoprotein and canine apoE-HDLc, both of which contain apolipoprotein E. Each of the seven cysteine-rich repeats in the ligand binding domain of the Xenopus receptors resembles its counterpart in the human, indicating that these repeats had already acquired their independent structures by the time of amphibian development. The cytoplasmic tail of both Xenopus receptors is 86% identical to the human, including the FDNPVY sequence necessary for internalization in coated pits. The attainment of a fully developed receptor structure in Xenopus suggests that earlier forms of the receptor may exist in animals that are older than amphibians. An accompanying paper demonstrates that expression of both Xenopus receptor genes is controlled by a sterol regulatory element that closely resembles the human sequence (Mehta, K.D., Brown, M.S., Bilheimer, D.W., and Goldstein, J.L. (1991) J. Biol. Chemical 266, 10415-10419).

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(FILE 'HOME' ENTERED AT 11:42:47 ON 13 FEB 2004)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 11:43:06 ON 13 FEB 2004

L1	23212	S "LDL RECEPTOR"
L2	14	S "LOW(A)DENSITY"
L3	237773	S LOW (A)DENSITY
L4	424929	S LIPOPROTEIN?
L5	3623226	S RECEPTOR?
L6	26576	S L4(A)L5
L7	18188	S L3(A)L6
L8	941	S "P42/44 MAPK"
L9	16	S L7 AND L8
L10	9	DUP REM L9 (7 DUPLICATES REMOVED)

L11	16	S L8 AND L6
L12	9	DUP REM L11 (7 DUPLICATES REMOVED)
L13	25	S L1 AND L8
L14	13	DUP REM L13 (12 DUPLICATES REMOVED)
		E MEHTA K D/AU
L15	128	S E3
L16	32841	S L1 OR L7
L17	60	S L15 AND L16
L18	21	DUP REM L17 (39 DUPLICATES REMOVED)